WO 2005/085245 PCT/GB2005/000885

CLAIMS:

## 1. A compound of formula (I):

$$\begin{array}{c|c}
R^{1'} & & & \\
X_{2} & & & \\
X_{3} & & & \\
X_{4} & & & \\
\end{array}$$

$$\begin{array}{c|c}
R^{1'} & & & \\
N - N & & \\
N - N & & \\
N - N & & \\
\end{array}$$

Ι

or a pharmaceutically acceptable salt thereof, wherein:

one of  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  is N and the others are C;

Y is -C(O)-,  $-S(O)_2$ -, or -C(NH)-;

Z is  $C_{1\text{--}4}$ alkylene, oxygen, -( $CH_2$ ) $_m$ O-, -O( $CH_2$ ) $_m$ -, -NR-, -( $CH_2$ ) $_m$ NR-,

-NR(CH<sub>2</sub>)<sub>m</sub>-, -(CH<sub>2</sub>)<sub>m</sub>S(O)<sub>2</sub>-, or a bond;

m is 1, 2, 3, or 4;

R is C<sub>0-4</sub>alkyl, C<sub>0-4</sub>alkylaryl, or C<sub>0-4</sub>alkylhetaryl;

R<sup>1</sup> and R<sup>1</sup> are each independently, halogen, hydroxy, cyano, C<sub>0-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

 $R^2$  is  $C_{0-4}$ alkyl,  $COOR^6$ ,  $COR^6$ ,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl–, hydroxy $C_{1-4}$ alkyl–, cycloalkyl $C_{0-4}$ alkyl–, aryl $C_{0-4}$ alkyl–, or hetaryl $C_{0-4}$ alkyl–, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $-N(C_{0-4}$ alkyl)( $C_{0-4}$ alkyl),  $-SO_2C_{1-4}$ alkyl,  $-SO_2N(C_{0-4}$ alkyl)( $C_{0-4}$ alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

 $R^3$  is hydrogen,  $-COOC_{0-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyl, aryl $C_{1-4}$ alkylthio—,  $-C_{0-4}$ alkylaryl,  $-C_{0-4}$ alkylhetaryl,  $-C_{0-4}$ alkylcycloalkyl, or  $-C_{0-4}$ alkylheterocyclyl, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano,  $C_{1-4}$ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl,  $-C_{0-4}$ alkylNHC(O)O( $C_{1-4}$ alkyl),  $-C_{0-4}$ alkylNR $^7$ R $^8$ , -C(O)R $^9$ ,  $C_{1-4}$ alkoxy $C_{0-4}$ alkyl—,  $-COOC_{0-4}$ alkyl,  $-C_{0-4}$ alkylNHC(O)R $^9$ ,  $-C_{0-4}$ alkylC(O)N(R $^{10}$ )<sub>2</sub>,  $-C_{1-4}$ alkoxyC<sub>1-4</sub>alkoxy, hydroxy $C_{0-4}$ alkyl—,  $-NHSO_2R^{10}$ ,  $-SO_2(C_{1-4}$ alkyl),  $-SO_2NR^{11}R^{12}$ , 5- to 6-membered heterocyclyl, phenyl $C_{0-2}$ alkoxy, or phenyl $C_{0-2}$ alkyl substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $-N(C_{0-4}$ alkyl)( $C_{0-4}$ alkyl),  $-SO_2C_{1-4}$ alkyl,  $-SO_2N(C_{0-4}$ alkyl)( $C_{0-4}$ alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo ( =O) substituent;

or  $R^3$  is  $-NR^4(-C_{0-4}alkylR^5)$ ;

 $R^4$  is  $C_{0-3}$ alkyl,  $-C_{2-3}$ alkyl- $NR^7R^8$ ,  $C_{3-6}$ cycloalkyl optionally substituted by hydroxy $C_{0-4}$ alkyl- further optionally substituted by hydroxy,  $C_{1-2}$ alkoxy $C_{2-4}$ alkyl-, or  $C_{1-2}$ alkyl- $S(O)_n$ - $C_{2-3}$ alkyl-;

n is 0, 1, or 2;

 $R^5$  is hydrogen, hydroxy $C_{2-3}$ alkyl-,  $C_{1-2}$ alkoxy $C_{0-4}$ alkyl-, or aryl, hetaryl, or heterocyclyl;

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wherein a heterocyclic nitrogen-containing  $R^5$  ring optionally is mono-substituted on the ring nitrogen with  $C_{1-4}$ alkyl, benzyl, benzyl,  $C_{1-4}$ alkyl-C(O)–,  $-SO_2C_{1-4}$ alkyl,  $-SO_2N(C_{0-4})$ alkyl)( $C_{0-4}$ alkyl),  $C_{1-4}$ alkoxycarbonyl, or aryl( $C_{1-4}$ alkoxy)carbonyl; and wherein the  $R^5$  rings are optionally mono-substituted on a ring carbon with halogen, cyano,  $C_{1-4}$ alkyl-C(O)–,  $C_{1-4}$ alkyl- $SO_2$ –,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, hydroxy,  $-N(C_{0-4}$ alkyl)( $C_{0-4}$ alkyl), hydroxy $C_{0-4}$ alkyl-, or  $C_{0-4}$ alkylcarbamoyl-, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

R<sup>6</sup> is C<sub>1-4</sub>alkyl, aryl, or hetaryl;

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R<sup>7</sup> and R<sup>8</sup> are independently C<sub>0-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, or CO(C<sub>1-4</sub>alkyl);

R<sup>9</sup> is C<sub>1-4</sub>alkyl, or C<sub>3-6</sub>cycloalkyl;

R<sup>10</sup> is C<sub>0-4</sub>alkyl, or C<sub>3-6</sub>cycloalkyl; and

R<sup>11</sup> and R<sup>12</sup> are independently C<sub>0-4</sub>alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R<sup>3</sup>.

- 2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein  $X_3$  is N.
- 3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein  $X_1$  is N.
  - 4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)- or  $-S(O)_2$ -.
  - 5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is  $C_{1-4}$ alkylene, oxygen,  $-(CH_2)_mO$ -, -NR- or a bond.
  - 6. A compound according to any one of the preceding claims 1, or a pharmaceutically acceptable salt thereof, wherein  $R^{I}$  and  $R^{I'}$  are each independently, hydrogen or halogen.
  - 7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein one of  $R^1$  and  $R^{1'}$  is hydrogen and the other is 5-chloro.
  - 8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein  $R^2$  is hydrogen.
  - 9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R<sup>3</sup> is hydrogen, -NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>(-C<sub>1-4</sub>alkylR<sup>5</sup>), aryl, hetaryl, or heterocyclyl wherein any of the rings is optionally substituted as defined in claim 1.
  - 10. A compound of formula (I) as defined in any one of Examples 1 to 25, or a pharmaceutically acceptable salt thereof.

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- 11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
- 12. A method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 13. A method for the treatment of hyperglycemia or diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 14. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 15. A method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
- 16. A compound of formula (IV):

 $\begin{array}{c|c}
R^{1'} & & H \\
 & X_{1} \\
 & X_{3} \\
 & X_{4} \\
 & H
\end{array}$ IV

wherein  $R^1$ ,  $R^{1'}$ ,  $R^2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  are as defined in claim 1, or a protected derivative thereof.